EXHIBIT 8

ORIGINAL ARTICLE

MAYO CLINIC

Severe Spruelike Enteropathy Associated With Olmesartan

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Abstract

Objective: To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension, in patients with unexplained severe spruelike enteropathy.

Patients and Methods: All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.

Results: The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d). The clinical presentation was of chronic diarrhea and weight loss (median, 18 kg; range, 2.5-57 kg), which required hospitalization in 14 patients (64%). Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in 15 patients, and marked subepithelial collagen deposition (collagenous sprue) in 7. Tissue transglutaminase antibodies were not detected. A gluten-free diet was not helpful. Collagenous or lymphocytic gastritis was documented in 7 patients, and microscopic colitis was documented in 5 patients. Clinical response, with a mean weight gain of 12.2 kg, was demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

Conclusion: Olmesartan may be associated with a severe form of spruelike enteropathy. Clinical response and histologic recovery are expected after suspension of the drug.

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Olmesartan is one of several angiotensin II receptor antagonists used for management of hypertension since 2002.[1] Diarrhea is a common adverse effect of many medications, although the mechanisms underlying diarrhea remain unclear in most cases. Enteropathy as a cause of drug-induced diarrhea has been reported previously with the use of azathioprine and mycophenolate mofetil.[2-4] We first suspected the possible connection between enteropathy and olmesartan when 2 consecutive patients referred to our institution for evaluation of presumed refractory celiac disease reported unexplained clinical improvement during hospitalization but prompt relapse following hospital discharge. They asked if the disease course could have been due to their hypertensive medications, which were withheld on hospitalization because of hypotension. At the same time, we were studying a cohort of patients with collagenous sprue and discovered olmesartan use in one-third of the patients with a recent diagnosis of the disorder.[5] As additional patients were identified with similar clinical features (eg, chronic diarrhea, weight loss, unexplained spruelike enteropathy with or without abnormal subepithelial collagen deposition, negative celiac serology, and lack of response to gluten exclusion), a perceived association between these features and olmesartan evolved. It also became clear that these patients were unlikely to have celiac disease, as all lacked IgA tissue transglutaminase antibodies and had never responded to a gluten-free diet. The clinical observation of improvement of gastrointestinal symptoms and subsequent demonstration of histologic recovery after olmesartan withdrawal prompted us to advise our patients with unexplained spruelike enteropathy to discontinue olmesartan. We reported our observation to US Food and Drug Administration officials and submitted reports using the MedWatch system.

In this article, we describe the clinical manifestations in 22 patients with unexplained spruelike enteropathy that improved clinically after discontinuation of olmesartan.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. Patients were considered for inclusion in the study if they had chronic diarrhea (>4 weeks) while taking olmesartan and met 2 additional criteria. First, the cause of their enteropathy

could not be established after a systematic diagnostic evaluation that included investigation for disorders associated with nonresponsive celiac disease as previously reported by our group.[6] Second, they had to improve clinically after discontinuation of olmesartan. Most of these patients had undergone extensive evaluation by their referring physicians and had had several therapeutic trials, without benefit. The electronic medical records of 24 such patients seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, were reviewed by one physician (M.L.H.). Two of the 24 patients were excluded from the study, 1 who had tropical sprue and 1 who improved clinically and histologically with oral budesonide before suspension of olmesartan.

Data Abstraction

Clinical and laboratory data were abstracted from the medical record. Only data that reflected conditions that existed before suspension of olmesartan were included as baseline data. We defined categories of body weight using body mass index and World Health Organization criteria.[7] Anemia was defined in women as a hemoglobin level of less than 12 g/dL (to convert to g/L, multiply by 10) and in men as a hemoglobin level of less than 13.5 g/dL. Hypoalbuminemia was defined as an albumin value lower than 3.5 g/dL (to convert to g/L, multiply by 10). HLA-DQ typing,[8] celiac disease serology (tissue transglutaminase antibodies or deamidated gliadin peptide antibodies by enzyme-linked immunosorbent assay and endomysial antibodies on monkey esophagus by indirect immunofluorescence),[9-11] and assessment of response to a gluten-free diet were investigated. Anti-enterocyte antibodies were tested using primate intestine by indirect immunofluorescence and were performed at The Children's Hospital of Philadelphia, as reported by Akram et al.[12] *Severe enteropathy* was defined by the presence of at least one of the following criteria: (1) need for hospitalization because of severe dehydration, electrolyte imbalance, and/or acute renal failure, (2) need for total parenteral nutrition, and (3) weight loss of more than 10 kg.

Histopathology

Pathology material (biopsy samples from the gastrointestinal tract) was reviewed by one of the authors (T.-T.W.). The number of intraepithelial lymphocytes per 100 epithelial cells, degree of villous atrophy graded with the modified Marsh classification,[13] presence of subepithelial collagen, degree of lamina propria inflammation, and presence of acute inflammation were assessed. The presence of aberrant or clonal intraepithelial lymphocytes was investigated by CD3 and CD8 immunostaining[14] and polymerase chain reaction,[15] respectively. When multiple small bowel biopsies were performed as part of the diagnostic evaluation and before withdrawal of the drug, the baseline biopsy was considered to be the small bowel biopsy performed closest to the date of suspension of olmesartan. Follow-up biopsies were defined as biopsies performed at least 30 days after the date of suspension of olmesartan. Other disorders of the gastrointestinal tract (when present) were diagnosed using accepted pathologic criteria (eg, microscopic colitis).[16]

Outcomes After Suspension of Olmesartan

Clinical response was defined as the resolution of diarrhea. Weight gain was considered a positive finding. *Remission* required both a clinical response and confirmation by normal findings on intestinal biopsy during follow-up. All patients who had been on a gluten-free diet were followed up after reintroduction of gluten and withdrawal of corticosteroids.

Medication Use

We reviewed the medication history of all patients, including the duration of treatment, dosage, and response of diarrhea to a trial of olmesartan withdrawal. Alternative antihypertensive drugs used after suspension of olmesartan are reported.

Statistical Analyses

Data were summarized using descriptive statistics, including total numbers and percentages for categorical variables and median or mean (range) for continuous variables.

RESULTS

The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Twenty-one of the patients were non-Hispanic white, and 1 patient was black. Patients were residents of 16 different US states (Table 1).

The most frequent clinical diagnoses at time of referral were nonresponsive/refractory celiac disease (n=10) and unexplained sprue (n=6). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d) for several months or years before the onset of diarrhea. Detailed information about the duration of exposure to olmesartan before onset of diarrhea was available in the medical record in 14 patients (64%). Among these, the mean duration was 3.1 years (range, 0.5-7 years). An additional 5 patients were taking olmesartan for at least 1 year before the onset of symptoms. Information about duration of exposure to olmesartan before onset of diarrhea was not available in 3 patients.

TABLE 1. Demographic Characteristics, Outcome, and Alternative Antihypertensive Drugs Used After Suspension of Olmesartan in 22 Patients With Spruelike Enteropathy

Patient No./ sex/age (y)	Weight loss (kg)	Outcome after suspension of olmesartan[a]	Alternative antihypertensive drug
1/F/59	14	Remission	Metoprolol
2/F/62	11	Clinical response	None
3/F/72	31	Remission, weight gain (13.3 kg)	Bisoprostol-hydrochlorothiazide
4/M/66[b]	18	Remission, weight gain (11 kg)	Metoprolol
5/M/81	2.5	Remission, weight loss (4.1 kg)	Lisinopril, metoprolol
6/M/64	14	Clinical response	Amlodipine
7/F/65	11	Remission, weight gain (4.2 kg)	Amlodipine, hydrochlorothiazide
8/M/76	12	Remission, weight gain (13.4 kg)	Amlodipine, hydrochlorothiazide
9/M/64	20.5	Remission, weight gain (15.7 kg)	Amlodipine, hydrochlorothiazide
10/F/72	30	Remission, weight gain (28 kg)	Amlodipine, atenolol, hydrochlorothiazide
11/M/74	15	Clinical response	Hydrochlorothiazide
12/M/58	57	Remission, weight gain (23.4 kg)	Amlodipine, metoprolol
13/F/77	29	Remission, weight gain (9.7 kg)	Atenolol, hydrochlorothiazide
14/F/76	7	Remission, weight gain (2.9 kg)	Hydrochlorothiazide
15/M/68	18	Remission, weight gain (14.9 kg)	Metoprolol
16/F/71	9	Remission, weight gain (11.9 kg)	Triamterene, hydrochlorothiazide
17/F/66[b]	20.5	Clinical response, weight gain (13.4 kg)	Spironolactone, carvedilol
18/F/64[c]	50	Clinical response, weight gain (4 kg)	Amlodipine
19/F/75	41	Remission	None
20/M/47	32	Remission, weight gain (13.9 kg)	Metoprolol, amlodipine, doxazosin
21/F/71	18	Remission, weight gain (10.2 kg)	Atenolol, hydralazine
22/F/74	40	Remission, weight gain (6.3 kg)	None

[a] Weight change (defined by weight at diagnosis minus weight at last follow-up visit) is provided when available in the medical record.
[b] Case previously published.
[c] Non-Hispanic black.

Clinical Manifestations

Diarrhea had been present for a median of 19.2 months (range, 3-53 months) before suspension of the drug. At the time of presentation, all patients had diarrhea and weight loss (median weight loss, 18 kg; range, 2.5-57 kg). Nausea and vomiting were present in 15 patients (68%), abdominal pain in 11 (50%), bloating in 9 (41%), and fatigue in 15 (68%). The onset of diarrhea was sudden in 9 patients. The stool frequency was extremely abnormal, with a median of 6 evacuations per day (range, 3-42 evacuations per day). Among 8 patients with timed stool collection, the mean stool weight was 933.1 g/24 h (range, 225-3225 g/24 h), and mean fecal fat was 28.3 g/24 h (range, 8-50 g/24 h). Although timed stool weight was not investigated in all patients, 14 patients (64%) required hospitalization because of severe dehydration (4 patients had acute renal failure). Total parenteral nutrition was necessary in 4 patients. At the time of the first visit at Mayo Clinic, 11 of the patients had normal weight, 6 were underweight, 4 were overweight, and 1 was obese. All but one patient (patient 16) met criteria for severe enteropathy.

Laboratory Findings

Results of IgA tissue transglutaminase antibody testing were negative in all patients. IgA endomysial antibody results were negative in all 9 patients who underwent testing. HLA-DQ typing was performed in 21 patients: DQ2 was present in 15 patients, DQ8 in 2 patients, and neither DQ2 nor DQ8 in 4 patients. Anti-enterocyte antibody testing was done in 19 patients (86%), and results were negative in 16 (including 7 patients who had a positive nonspecific nuclear pattern of unknown clinical significance) and positive with a linear/apical pattern in 3.

Fourteen patients (64%) had normocytic normochromic anemia (2 had elevated red blood cell distribution width suggesting anisocytosis); the lowest hemoglobin level was 9.3 g/dL. Ten patients (45%) had hypoalbuminemia; the lowest albumin

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level was 2 g/dL. Twelve patients (55%) had one (n=3) or multiple (n=9) electrolyte abnormalities. Zinc deficiency was documented in 7 patients.

Small bowel bacterial overgrowth was confirmed by culture of duodenal aspirate (>10^5 colony-forming units per milliliter) in 12 patients at some point during clinical evolution. A trial of oral antibiotics was used in 10 patients without clinical benefit (rifaximin in 5, tetracycline in 3, ciprofloxacin in 1, and ciprofloxacin-metronidazole in 1). An additional 2 patients received no therapy for small bowel bacterial overgrowth.

Histologic Findings

In all patients, baseline intestinal biopsies demonstrated villous atrophy with variable degrees of mucosal inflammation (Table 2). Total villous atrophy was observed in 15 patients and partial villous atrophy in 7 patients. A thick band of subepithelial collagen deposition (collagenous sprue) was seen in 7 patients (2 cases had been reported previously [9]). Active/acute inflammation was observed in 15 patients, and increased intraepithelial lymphocytes were found in 14 patients. Aberrant (or clonal) intraepithelial lymphocytes were not detected among the 12 patients tested.

Colonoscopy with random colonic biopsies was performed in 13 patients (59%). Microscopic colitis was found in 5 patients (2 had lymphocytic colitis and 3 had collagenous colitis).

Biopsies of the stomach were available in 14 patients (64%). Lymphocytic gastritis was diagnosed in 5 patients and collagenous gastritis in 2 patients. Chronic gastritis was diagnosed in an additional 7 patients (1 had *Helicobacter pylori* infection).

Treatment and Subsequent Course

Most of the patients in our study had undergone several therapeutic trials, without apparent clinical benefit, before referral to Mayo Clinic, including the use of a gluten-free diet for months (n=20), systemic corticosteroids and/or budesonide (n=20), opioid-derived antidiarrheal agents (most often loperamide) (n=10), pancreatic enzymes (n=4), bile acid sequestrant (n=4), metronidazole (n=4), azathioprine (n=3), and octreotide (n=3).

Clinical response was observed in all 22 patients after suspension of olmesartan. Besides tapering of corticosteroids, no medication was needed to control diarrhea after clinical response was achieved with suspension of the drug. Patients following a gluten-free diet were advised to abandon the diet immediately if they lacked the celiac susceptibility genotypes or to gradually reintroduce gluten if they were HLA-DQ2 or DQ8 positive. No patient had recurrence of symptoms after restarting a gluten-containing diet. Follow-up body weight after suspension of olmesartan was available in 17 patients; 16 had weight gain, with a mean weight gain of 12.2 kg (range, 2.9-28 kg), and 1 patient (patient 5) who had edema at diagnosis lost 4.1 kg during follow-up despite clinical remission.

At the time of this report, follow-up intestinal biopsies have been performed in 18 patients (82%) after a mean of 242.3 days (range, 54-707 days) from the date of suspension of olmesartan. Histologic recovery of the duodenum was documented in 17 patients (Figure). Focal partial villous atrophy was observed in 1 case (patient 2) on a follow-up duodenal biopsy obtained 54 days after suspension of olmesartan. Follow-up gastric biopsies were performed at the same time as repeated biopsy of the duodenum in 6 of the 7 patients with either lymphocytic or collagenous gastritis (no gastric biopsy results were available for patient 11). Follow-up gastric biopsies showed normal mucosa in 4 patients and nonspecific mild chronic gastritis in 2 patients (patients 20 and 22). Follow-up colonoscopies with biopsies of the colon were not performed in the 5 patients with microscopic colitis.

DISCUSSION

We describe a group of patients with unexplained severe spruelike enteropathy while taking olmesartan. We also provide evidence of both clinical and histologic improvement after suspension of olmesartan. Celiac disease was excluded by conventional methods of serology and the absence of clinical response to a gluten-free diet.[10] Other less common enteropathies were excluded (Table 3).

We acknowledge that this case series lacks all the information necessary to prove causality but rather reflects an association. No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan. Resolution of the presenting symptoms and subsequent histologic improvement after suspension of olmesartan, in the absence of clinical evidence of other diseases associated with enteropathy, suggest that the association is not likely to be due to chance.

Pathologic findings in the duodenal biopsy can mimic celiac disease or collagenous sprue. Clinicopathologic correlation is advised to confirm the diagnosis of olmesartan-associated enteropathy. Pathologic evidence of involvement of other organs (eg, the

TABLE 2. Histologic Findings in 22 Patients With Sprueliike Enteropathy Associated With Olmesartan[a]

Patient No.	Baseline duodenal biopsy results					Outcome follow-up duodenal biopsy results	Time d[d]	Other GI findings[e]	
	Villous atrophy	IELs (/100 epithelial cells)[b]	Acute/active inflammation	Thickened collagen band	Aberrant cells/clone[c]			Gastric	Colorectal
1	Total	Normal	Yes	No	No/No	Normal	404	Lymphocytic gastritis (HP negative, immunostain)	Collagenous colitis
2	Total	80-100	Yes	Yes	No/NA	Improvement, focal partial villous atrophy	54	Chronic gastritis (HP negative, immunostain)	Normal
3	Total	Normal	Yes	No	No/No	Normal	231	NA	Collagenous colitis
4	Total	40	Yes	Yes	No/No	Normal	263	Collagenous gastritis	NA
5	Total	>100	Yes	No	NA/NA	Normal	54	NA	Normal
6	Partial	60	Yes	No	NA/NA	NA	NA	NA	NA
7	Partial	>100	No	No	No/No	Normal	159	NA	Normal
8	Total	40-60	Yes	No	NA/NA	Normal	143	Lymphocytic gastritis (HP negative, immunostain)	Normal
9	Total	60-80	Yes	No	No/No	Normal	188	NA	NA
10	Partial	Normal	No	No	No/No	Normal	404	NA	NA
11	Partial	50	Yes	No	No/No	NA	NA	Mild lymphocytic gastritis (HP negative, immunostain)	NA
12	Partial	Normal	Yes	No	No/No	Normal, focal active duodenitis	116	Mild active chronic gastritis (HP negative, immunostain)	Mild active chronic colitis
13	Total	40	Yes	Yes	NA/NA	Normal	171	Active chronic gastritis (HP negative, immunostain)	NA
14	Partial	60-80	No	No	NA/NA	Normal	240	Mild active chronic gastritis (HP negative, immunostain)	NA
15	Total	Normal	No	Yes	NA/NA	Normal	181	Mild chronic gastritis (HP negative, no immunostain)	Normal
16	Total	Normal	No	Yes	No/No	Normal	607	Collagenous gastritis	Collagenous colitis
17	Total	40-60	Yes	Yes	No/No	NA	NA	Mild chronic gastritis (HP negative, no immunostain)	Focal acute colitis
18	Partial	Normal	No (marked eosinophilia)	No	NA/NA	NA	NA	NA	NA
19	Total	30	Yes	No	NA/NA	Normal	76	Severe active chronic gastritis and ulceration (HP negative, immunostain)	NA
20	Total	Normal	No	Yes	No/No	Normal	707	Lymphocytic gastritis (HP positive)	Lymphocytic colitis
21	Total	80-100	Yes	No	NA/NA	Normal	179	NA	Lymphocytic colitis
22	Total	80	Yes	No	NA/NA	Normal	184	Lymphocytic gastritis (HP negative, immunostain)	Normal

[a] HP = *Helicobacter pylori*; IELs = intraepithelial lymphocytes; NA = not available.
[b] Normal, <25/100 epithelial cells.
[c] Aberrant cells defined by >50% $CD3^+/CD8^-$ IELs on immunostaining; clone defined by T-cell receptor gene clonal rearrangement by polymerase chain reaction.
[d] Time from suspension of olmesartan to follow-up biopsy.
[e] Any time before suspension of olmesartan.

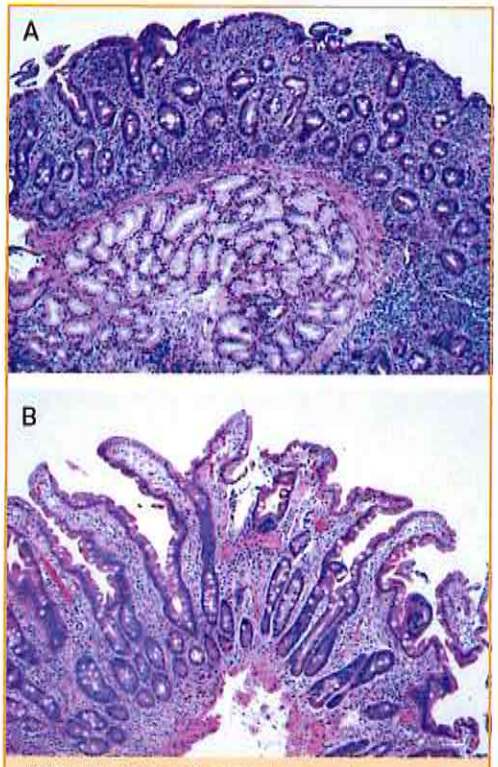

FIGURE. Photomicrographs showing reversible spruelike enteropathy associated with olmesartan (hematoxylin-eosin, original magnification ×100). A, Duodenal biopsy specimen obtained while the patient was taking olmesartan shows total villous atrophy and intraepithelial lymphocytosis. B, Biopsy specimen obtained 6 months after withdrawal of olmesartan and initiation of a gluten-containing diet shows recovery of villi on duodenal mucosa.

stomach and colon) suggests that this disorder may affect the entire gastrointestinal tract. We provide evidence of resolution of inflammation and/or fibrosis in the stomach and duodenum after suspension of olmesartan, implying that these changes are associated with the use of olmesartan. Even though follow-up colonoscopies were not performed in the 5 patients with documented microscopic colitis, clinical remission was achieved in all of these patients, a very unlikely outcome in the presence of persistent inflammation or fibrosis of the colon. Recovery of duodenal mucosa in a relatively short time (median of 8 months from suspension of olmesartan to follow-up biopsies) is a relevant clinical observation because mucosal recovery in other small bowel disorders, such as celiac disease, may take years to occur despite adherence to a gluten-free diet, especially in older adults.[18,19]

Finding small bowel bacterial overgrowth in 12 patients is intriguing and consistent with prior observations of association of small bowel bacterial overgrowth and enteropathy in symptomatic patients with celiac disease.[20,21] The reason for this association is unknown. Thus, although small bowel bacterial overgrowth is a well-recognized cause of chronic diarrhea in the right clinical setting,[22] in this series, the lack of clinical response to oral antibiotics suggests that gastrointestinal symptoms are not explained by the effects of an increased number of bacteria in the small bowel.

The mechanisms underlying olmesartan-associated enteropathy are unknown. The long delay between onset of olmesartan therapy and the development of diarrhea (and enteropathy) suggests cell-mediated immunity damage rather than type I hypersensitivity. Recently, angiotensin receptor blockers have been suggested to have inhibitory effects on transforming growth factor β action.[23,24] Transforming growth factor β is crucially important in the maintenance of gut immune homeostasis.[25,26] Olmesartan is an orally administrated prodrug (olmesartan medoxomil) that is rapidly metabolized to the active component (olmesartan) by esterases in the gastrointestinal mucosa, portal blood, and liver.[27] Nevertheless, the possible role of transforming growth factor β inhibition in olmesartan-associated enteropathy is a question that requires investigation. We do not know if other angiotensin II receptor blockers can be associated with a similar form of enteropathy, but active investigation for similar cases among patients using other drugs of the same class is under way. All our patients with olmesartan-associated enteropathy received antihypertensive drugs from a different class after suspension of olmesartan. HLA-DQ2 was present in 68% of patients with olmesartan-associated enteropathy, a prevalence higher than the 25% to 30% expected for the general population,[28,29] suggesting that perhaps

TABLE 3. Clinical Features of Spruelike Enteropathy Associated With Olmesartan

Gastrointestinal symptoms (eg, chronic diarrhea, weight loss, steatorrhea)
Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
Lack of clinical response to gluten exclusion
Exclusion of other causes of enteropathy (eg, celiac disease)
Evidence of clinical and histologic improvement after suspension of olmesartan

the presence of HLA-DQ2 may increase the risk of immune-mediated damage in these patients. This may be another example of drug-associated enteropathy of which the medical community should be aware and could result in the identification of several more cases.

CONCLUSION

We report a unique case series to support a novel association between severe spruelike enteropathy and olmesartan. Physicians who encounter patients with diarrheal syndromes should consider medications as a cause, although the potential role for olmesartan had not been considered in these patients by any of the physicians prescribing the medications or treating the diarrheal illness.

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EXHIBIT 9

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil

Safety Announcement

[7-3-2013] The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. FDA has approved changes to the labels of these drugs to include this concern.

Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization (see Data Summary). If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.

FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available.

FACTS about Olmesartan

- Olmesartan is an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and heart attacks.
- In 2012, a total of approximately 10.6 million prescriptions were dispensed, and approximately 1.9 million patients received a dispensed prescription for olmesartan-containing products from U.S. outpatient retail pharmacies.[1] According to sales data, the majority of olmesartan-containing products were distributed to outpatient retail pharmacies (81.5% retail, 15% mail order/specialty pharmacies and 3.5% non-retail) during this time.[2]

Additional Information for Patients

- Contact your health care professional right away if you take an olmesartan-containing product and experience severe diarrhea, diarrhea that does not go away, or significant weight loss.
- Your health care professional may evaluate your symptoms to determine the cause. If no other cause is found, you may be asked to stop taking olmesartan and start taking a different high blood pressure medicine.
- Do not stop taking your high blood pressure medicine without first discussing it with your health care professional. When high blood pressure is not appropriately treated, strokes, heart attacks or kidney failure, or other serious harm can result.
- Discuss any questions or concerns about olmesartan with your health care professional.
- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Tell your patients to contact you if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop.
- If a patient develops these symptoms during treatment with olmesartan, other etiologies, such as celiac disease, should be investigated. If no other etiology is identified, olmesartan should be discontinued and another antihypertensive treatment started.
- Symptoms of sprue-like enteropathy may develop months to years after starting olmesartan.
- Report adverse events involving olmesartan-containing products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) that was approved on April 25, 2002, for the treatment of hypertension, alone or with other antihypertensive agents. The current olmesartan drug labels include diarrhea in the Adverse Reactions section.

FDA evaluated adverse event reports received by FDA's Adverse Event Reporting System (FAERS), published literature case series,[3-4] information from FDA's Mini-Sentinel pilot of the Sentinel Initiative, and information from the CMS Medicare database. FDA's evaluation found clear evidence of an association between olmesartan and sprue-like enteropathy.

FDA identified 23 serious cases in FAERS presenting as late-onset diarrhea with significant weight loss and, in some cases, with intestinal villous atrophy on biopsy. All patients improved clinically after discontinuation of olmesartan, and a positive rechallenge was seen in 10 of the cases.

In June 2012, Mayo Clinic researchers published a case series of sprue-like enteropathy associated with olmesartan in 22 patients whose clinical presentation was similar to that of the FAERS cases: Patients in the Mayo Clinic case series developed diarrhea, weight loss, and villous atrophy while on olmesartan, and drug discontinuation resulted in clinical improvement.[3] Eighteen patients had follow-up intestinal biopsies histologically demonstrating recovery or improvement of the duodenum after discontinuation of olmesartan.

In May 2013, an article describing patients with villous atrophy and negative serologies for celiac disease reported that some patients without definitive etiologies for villous atrophy were characterized as having unclassified sprue. Some of these patients were later found to have villous atrophy associated with olmesartan use.[4]

The signal of sprue-like enteropathy with olmesartan was further investigated for a possible ARB class effect using active surveillance data. Mini-Sentinel and CMS Medicare data were assessed for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs. Mini-Sentinel and CMS Medicare assessments of ICD-9 codes for celiac disease showed that at a 2-year minimum exposure, which correlates with the long latency observed in literature and case reports, olmesartan users had a higher rate of celiac disease diagnoses in claims and administrative data than users of other ARBs. Interpretation is limited by the small number of events observed at longer exposure periods and the uncertainty about the validity of codes for celiac disease, but these results support other data in suggesting a lack of a class effect.

Although the mechanism for olmesartan-associated sprue-like enteropathy is uncertain, the long latency before onset of symptoms, findings of lymphocytic or collagenous colitis, and high association with HLA-DQ2/8 suggest a localized delayed hypersensitivity or cell-mediated immune response to the pro-drug olmesartan medoxomil. Rubio-Tapia et al., suggest that ARB-mediated inhibition of TGF-β, an important mediator of gut homeostasis, is a possible mechanism for olmesartan-associated sprue-like enteropathy, although it is unclear why this effect is not observed with other ARBs.[3]

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EXHIBIT 10

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Microalbuminuria is an early predictor of diabetic nephropathy and premature cardiovascular disease. We investigated whether treatment with an angiotensin-receptor blocker (ARB) would delay or prevent the occurrence of microalbuminuria in patients with type 2 diabetes and normoalbuminuria.

METHODS

In a randomized, double-blind, multicenter, controlled trial, we assigned 4447 patients with type 2 diabetes to receive olmesartan (at a dose of 40 mg once daily) or placebo for a median of 3.2 years. Additional antihypertensive drugs (except angiotensin-converting–enzyme inhibitors or ARBs) were used as needed to lower blood pressure to less than 130/80 mm Hg. The primary outcome was the time to the first onset of microalbuminuria. The times to the onset of renal and cardiovascular events were analyzed as secondary end points.

RESULTS

The target blood pressure (<130/80 mm Hg) was achieved in nearly 80% of the patients taking olmesartan and 71% taking placebo; blood pressure measured in the clinic was lower by 3.1/1.9 mm Hg in the olmesartan group than in the placebo group. Microalbuminuria developed in 8.2% of the patients in the olmesartan group (178 of 2160 patients who could be evaluated) and 9.8% in the placebo group (210 of 2139); the time to the onset of microalbuminuria was increased by 23% with olmesartan (hazard ratio for onset of microalbuminuria, 0.77; 95% confidence interval, 0.63 to 0.94; P=0.01). The serum creatinine level doubled in 1% of the patients in each group. Slightly fewer patients in the olmesartan group than in the placebo group had nonfatal cardiovascular events — 81 of 2232 patients (3.6%) as compared with 91 of 2215 patients (4.1%) (P=0.37) — but a greater number had fatal cardiovascular events — 15 patients (0.7%) as compared with 3 patients (0.1%) (P=0.01), a difference that was attributable in part to a higher rate of death from cardiovascular causes in the olmesartan group than in the placebo group among patients with preexisting coronary heart disease (11 of 564 patients [2.0%] vs. 1 of 540 [0.2%], P=0.02).

CONCLUSIONS

Olmesartan was associated with a delayed onset of microalbuminuria, even though blood-pressure control in both groups was excellent according to current standards. The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern. (Funded by Daiichi Sankyo; ClinicalTrials.gov number, NCT00185159.)

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DIABETIC NEPHROPATHY IS AN INCREASINGLY common cause of end-stage renal disease,[1] and the development and rate of renal deterioration are most closely related to the patient's blood pressure. Guideline committees worldwide concur that the blood pressure in patients with diabetes and chronic kidney disease should be kept at 130/80 mm Hg or less.[2] Microalbuminuria is predictive of diabetic nephropathy and premature cardiovascular disease[3-5]; therefore, European and American guidelines recommend that patients with diabetes be tested for microalbuminuria.[6,7]

Overactivity of the renin–angiotensin system has been implicated in the deterioration of renal function in patients with diabetic nephropathy and in patients who have stage 3 or 4 chronic kidney disease with microalbuminuria or macroalbuminuria.[8,9] Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) slow the worsening of the glomerular filtration rate (GFR) and lower the rate of albumin excretion. Treatment at an early stage of the disease may be beneficial. ACE inhibition delays the onset of microalbuminuria in patients with hypertension, type 2 diabetes, normoalbuminuria, and normal renal function.[10] Whether similar benefits occur when ARB therapy is begun early in the course of diabetes is unknown.[11,12]

In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, we tested whether olmesartan medoxomil (Benicar, Daiichi Sankyo), at a dose of 40 mg daily, as compared with placebo, prevents or delays the time to the first occurrence of microalbuminuria in patients who have type 2 diabetes, as well as at least one other cardiovascular risk factor, and normoalbuminuria. Blood-pressure control (<130/80 mm Hg) in both groups was achieved by adding, as needed, antihypertensive agents that do not block the renin–angiotensin system.

METHODS

STUDY DESIGN AND ORGANIZATION

The study design has been published previously.[13] The sponsor (Daiichi Sankyo) had no role in the design or conduct of the study, but representatives of the sponsor served as nonvoting members of the steering committee. Statistical analyses were performed by a clinical research organization, with confirmation by biostatisticians who were employees of the sponsor. The authors had complete control over the analysis and interpretation of the results, the writing of the manuscript, and the decision to submit it for publication, and they vouch for the accuracy and completeness of the reported data, as well as the fidelity of the reported study to the protocol. The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

We conducted this randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3b study at 262 collaborating centers in 19 European countries. The ethics committee at each participating center approved the study, and written informed consent was obtained from each patient. The study enrolled patients with type 2 diabetes, among whom there was a wide range of blood-pressure values, including some that were in the normal range. Patients who had used ACE inhibitors or ARBs during the 6 months before the start of the study were excluded. Treatment with ACE inhibitors and ARBs (other than olmesartan in the experimental group) was not allowed at any time during the study; during the double-blind treatment phase, other antihypertensive agents were allowed in both groups to help patients reach and maintain the target blood pressure of less than 130/80 mm Hg.

STUDY POPULATION

A total of 4449 white patients, 18 to 75 years of age, who had type 2 diabetes underwent randomization. A summary of the main inclusion and exclusion criteria and an overview of the screening, enrollment, randomization, and follow-up are shown in Tables 1 and 2 in the Supplementary Appendix, available at NEJM.org. After the screening phase, each patient's eligibility for the study was established during a prerandomization phase (maximum duration, 4 weeks), during which normoalbuminuria was confirmed by means of two additional measurements of morning spot urine samples.

END POINTS

The primary end point was the time to the first onset of microalbuminuria, as determined by validated measurements of morning spot urine samples. Microalbuminuria was defined as a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of more than 35 in women or more than

25 in men. Any single elevation in the urinary albumin-to-creatinine ratio required confirmation by at least one additional positive result from two separate tests of urine samples performed within 2 weeks after the initial test. If microalbuminuria was confirmed, the patient was assigned to an open-label phase in which he or she received olmesartan at a dose of 40 mg daily (Fig. 1 in the Supplementary Appendix). At each follow-up visit, a spot urine sample was obtained, and blood pressure was measured with an automatic device. The blood-pressure measurement that was used was the mean of three values recorded 3 minutes apart. If the blood pressure was 130/80 mm Hg or higher, the protocol called for adjustment of the antihypertensive medication (excluding the use of blockers of the renin–angiotensin system or aldosterone blockers). A central laboratory (CRL-Medinet) determined the urinary albumin-to-creatinine ratio and all other laboratory variables. Secondary end points included a composite of cardiovascular complications and death from cardiovascular causes (Table 3 in the Supplementary Appendix) and renal events.

STATISTICAL ANALYSIS

A total of 4447 of the 4449 patients who underwent randomization were included in the intention-to-treat analysis; 2 patients who underwent randomization never took a study medication (Table 2A in the Supplementary Appendix). The baseline urinary albumin-to-creatinine ratio was the geometric mean of three measurements obtained during the randomization phase (up to visit 1). A confirmatory analysis of the primary efficacy end point was performed with the use of a Cox proportional-hazards regression model with treatment as a fixed effect; the baseline urinary albumin-to-creatinine ratio was logarithmically transformed (base 10) as a covariate, and a two-tailed Wald chi-square test was performed with an alpha level of less than 0.05; hazard ratios and two-sided 95.1% confidence intervals were calculated. (Owing to a prespecified interim analysis performed by the data and safety monitoring board, the significance level for the final confirmatory analysis was adjusted to 0.049, resulting in a two-sided 95.1% confidence interval.) To account for all patients who entered the double-blind treatment period, the last assessment that was performed before patients left the double-blind period was used as the last time point. All statistical analyses were performed with the use of SAS software for Windows, version 9.1.3 (SAS Institute); values are expressed as means ±SD unless otherwise indicated. Section 1 in the Supplementary Appendix includes additional information regarding the calculation of the sample size and other statistical methods.

RESULTS

STUDY PATIENTS

Recruitment began in October 2004 and was completed in May 2006. After the prespecified number of adjudicated microalbuminuria events was reached, the study was stopped. The last evaluation for any patient occurred in June 2009; the median follow-up period was 3.2 years. The baseline data for participants are summarized in Table 1. The mean duration of diabetes was 6.1 years, and the mean glycated hemoglobin level was 7.7%. More than 97% of the patients had at least two cardiovascular risk factors in addition to type 2 diabetes, and 67.7% had at least four.

BLOOD-PRESSURE CONTROL

The mean blood pressure during the follow-up period was 125.7/74.3 mm Hg in the olmesartan group and 128.7/76.2 mm Hg in the placebo group (Fig. 2A in the Supplementary Appendix). Nearly 80% of the patients in the olmesartan group and about 71% of the patients in the placebo group had a blood pressure of less than 130/80 mm Hg (the target) at month 48 (Fig. 2B in the Supplementary Appendix).

At the end of the study, 24-hour ambulatory blood-pressure monitoring was performed in 568 patients (270 in the olmesartan group and 298 in the placebo group). Over the course of the study, blood pressure, as measured both in the clinic and by means of 24-hour ambulatory blood-pressure monitoring, was lower in the olmesartan group than in the placebo group (by 3.3/1.3 mm Hg in clinic measurements and by 3.5/1.2 mm Hg with 24-hour ambulatory blood-pressure monitoring).

PRIMARY END POINT

During the double-blind treatment period, microalbuminuria developed in 178 of 2160 patients in the olmesartan group for whom measurements of urinary albumin-to-creatinine ratio could be evaluated (8.2%) and 210 of 2139 patients in the

placebo group for whom measurements of urinary albumin-to-creatinine ratio could be evaluated (9.8%); the median time to the onset of microalbuminuria was 576 days in the placebo group and 722 days in the olmesartan group. The primary end point, the time to the onset of microalbuminuria (Fig. 1), was increased by 23% with olmesartan (hazard ratio for onset of microalbuminuria, 0.77; 95.1% confidence interval [CI], 0.63 to 0.94; P=0.01). After adjustment for small baseline differences in the body-mass index, systolic blood pressure, and levels of high-density lipoprotein cholesterol and triglycerides (Table 1), the hazard ratio for the primary end point was 0.75 (95.1% CI, 0.62 to 0.92; P=0.006). Similar results were obtained in a prespecified per-protocol analysis and in a post hoc analysis that excluded patients who discontinued the study treatment prematurely (Table 4 in the Supplementary Appendix). The reduction in the primary end point with olmesartan remained after adjustment for differences in blood-pressure levels (Fig. 2). To identify other factors influencing the response to olmesartan treatment, an exploratory post hoc subgroup analysis was performed for several known risk factors, with dichotomization at the median for each candidate predictor variable. Baseline characteristics associated with a favorable response to olmesartan therapy included systolic blood pressure higher than 135 mm Hg, a glycated hemoglobin level of 7.3% or less, an estimated GFR of 83.79 ml per minute per 1.73 m² of body-surface area or less, and a urinary albumin-to-creatinine ratio of more than 4 (Fig. 2).

SECONDARY END POINTS

Renal Function

The mean estimated GFR declined from 85.0±17.0 ml per minute per 1.73 m² at baseline to 80.1±18.5 ml per minute per 1.73 m² at the last assessment

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Olmesartan (N=2232)	Placebo (N=2215)	Total (N=4447)	P Value
Male sex — no. (%)	1049 (47.0)	1003 (45.3)	2052 (46.1)	0.25†
Age				
Mean — yr	57.7±8.8	57.8±8.6	57.7±8.7	0.74‡
≥65 yr — no. (%)	564 (25.3)	554 (25.0)	1118 (25.1)	0.84†
Body-mass index§	31.1±4.9	30.9±4.9	31.0±4.9	0.05‡
Diabetes				
Duration — yr	6.2±6.0	6.1±6.0	6.1±6.0	0.60‡
Prior treatment — no. (%)	2072 (92.8)	2069 (93.4)	4141 (93.1)	0.45†
Smoking status — no. (%)				0.91†
Never smoked	1367 (61.2)	1343 (60.6)	2710 (60.9)	
Former smoker	452 (20.3)	453 (20.5)	905 (20.4)	
Current smoker	413 (18.5)	419 (18.9)	832 (18.7)	
Metabolic syndrome — no. (%)¶	1834 (82.2)	1797 (81.1)	3631 (81.7)	0.37†
Cardiovascular history — no. (%)				
Coronary heart disease	564 (25.3)	540 (24.4)	1104 (24.8)	0.49†
Myocardial infarction	134 (6.0)	119 (5.4)	253 (5.7)	0.36†
Stroke or TIA	55 (2.5)	49 (2.2)	104 (2.3)	0.58†
Peripheral vascular disease	17 (0.8)	8 (0.4)	25 (0.6)	0.07†
Glucose — mmol/liter	9.0±3.1	9.0±3.1	9.0±3.1	1.00‡
Glycated hemoglobin — %	7.7±1.6	7.7±1.6	7.7±1.6	0.89‡
Blood pressure while seated — mm Hg				
Systolic	137±16	136±15	136±15	0.02‡
Diastolic	81±10	80±9	81±10	0.11‡

Table 1. (Continued.)

Characteristic	Olmesartan (N=2232)	Placebo (N=2215)	Total (N=4447)	P Value
Urinary albumin-to-creatinine ratio‖				
Geometric mean	6.3±7.6	5.9±6.7	6.1±7.2	0.06‡
Median	4	3	4	
Interquartile range	2–7	2–7	2–7	
Serum creatinine — μmol/liter	77.4±15.2	77.5±17.1	77.5±16.2	0.96‡
Estimated GFR**				
Mean — ml/min/1.73 m²	85.0±17.0	84.7±17.3	84.9±17.2	0.60‡
<60 ml/min/1.73 m² — no. (%)	138 (6.2)	120 (5.4)	258 (5.8)	0.28†
Cholesterol — mmol/liter				
Total	5.2±1.1	5.2±1.1	5.2±1.1	0.76‡
LDL	3.1±0.9	3.1±0.9	3.1±0.9	0.31‡
HDL	1.20±0.30	1.22±0.30	1.21±0.30	0.02‡
Triglycerides — mmol/liter	2.1±1.7	2.0±1.3	2.1±1.5	0.02‡

* Plus–minus values are means ±SD. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and TIA transient ischemic attack.
† Exploratory comparisons were performed with the use of a chi-square test.
‡ Exploratory comparisons were performed with the use of Student's t-test.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).
‖ Albumin was measured in milligrams, and creatinine in grams. The baseline urinary albumin-to-creatinine ratio was defined as the geometric mean of the last three measurements that could be evaluated at the time of visit 1 (baseline). If insufficient measurements were available at baseline, the last measurements from the screening period were used.
** The estimated glomerular filtration rate (GFR) was calculated with the use of the abbreviated Modification of Diet in Renal Disease formula.

in the olmesartan group and from 84.7±17.3 ml per minute per 1.73 m² to 83.7±18.3 ml per minute per 1.73 m² in the placebo group (P<0.001 for the between-group comparison of the change from baseline). End-stage renal disease did not develop in any patient; the number of patients in whom there was a doubling of the serum creatinine level was the same in each group (23 patients, or approximately 1%).

Cardiovascular End Points

The proportion of patients who reached the composite end point of cardiovascular complications or death from cardiovascular causes was similar in the two groups — 96 of 2232 patients (4.3%) in the olmesartan group and 94 of 2215 patients (4.2%) in the placebo group (Table 2). The rate of death from any cause was also very low — 1.2% (26 deaths) among patients taking olmesartan and 0.7% (15) among patients taking placebo (P=0.10); in no case did the investigator report that the death was related to the study medication. The number of deaths from cardiovascular causes was higher in the olmesartan group than in the placebo group (15 vs. 3, P=0.01) (Table 2), owing primarily to more cases of fatal myocardial infarction (5 vs. 0) and sudden cardiac deaths (7 vs. 1) in the olmesartan group. The majority of deaths from cardiovascular causes (12 of 18) occurred in the subgroup of 1104 patients who had preexisting coronary heart disease. A post hoc analysis revealed an interaction between study group and preexisting coronary heart disease; among patients with preexisting coronary heart disease, there were 11 deaths from cardiovascular causes in the olmesartan group as compared with 1 in the placebo group (6.9 vs. 0.7 events per 1000 person-years, P=0.02) (Table 5 in the Supplementary Appendix). A further exploratory analysis showed additional interactions: among pa-

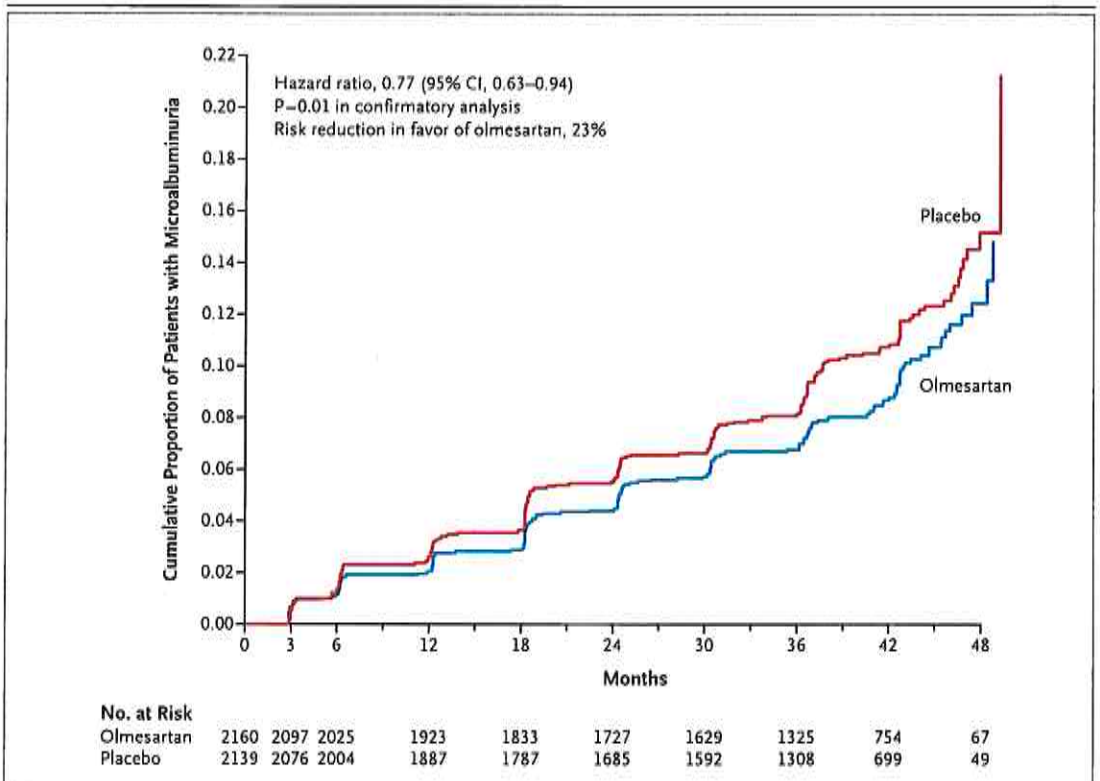

Figure 1. Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups.
The restricted full analysis set was used for this analysis. This set comprises all patients from the full analysis set (i.e., patients in the intention-to-treat population) with the exception of patients who had confirmed microalbuminuria at baseline (visit 1) and patients without any follow-up measurements of microalbuminuria that could be evaluated.

tients with preexisting coronary heart disease, those in the lowest quartile of systolic blood pressure and those in the highest quartile of reduction in systolic blood pressure during the double-blind treatment period had the highest rates of death from cardiovascular causes (Fig. 3 in the Supplementary Appendix). No interactions with diastolic blood pressure were detected. The rate of nonfatal cardiac events was reduced with olmesartan as compared with placebo among patients without preexisting coronary heart disease but not among those with preexisting coronary heart disease (Table 5 in the Supplementary Appendix).

ADVERSE EVENTS

The number of participants in whom adverse events occurred during the treatment period was similar in the two groups (Table 3). Serious adverse events were reported in 335 patients (15.0%) in the olmesartan group and 337 (15.2%) in the placebo group. Drug-related adverse events occurred in 255 patients (11.4%) receiving olmesartan and 166 (7.5%) receiving placebo (P<0.001). This difference was due in part to a higher rate in the olmesartan group than in the placebo group of hypotension (58 patients vs. 6, P<0.001) and dizziness (103 vs. 61, P=0.001). More patients in the olmesartan group than in the placebo group were withdrawn from the study because of symptomatic hypotensive episodes (10 patients vs. 1).

DISCUSSION

There is convincing epidemiologic evidence that in patients with diabetes who also have microalbuminuria, renal impairment and cardiovascular events occur earlier than they do in patients with diabetes who do not have microalbuminuria.[14-16] In this study, ARB-based therapy in patients with type 2 diabetes increased the time to the onset of microalbuminuria by 23%. The baseline characteristics of patients who were most likely to benefit from ARB therapy included a higher systolic blood pressure (≥135 mm Hg) before treatment,

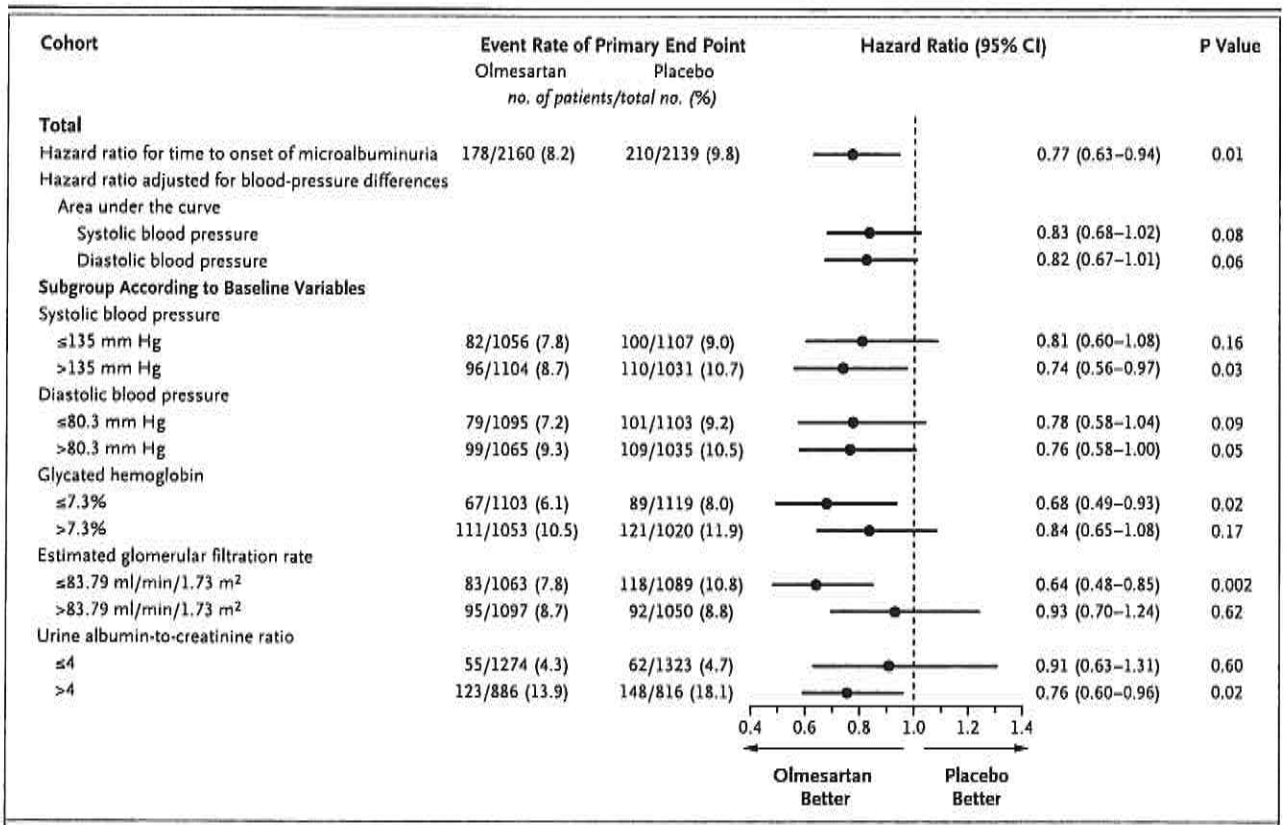

Figure 2. Event Rate of the Primary End Point in the Two Study Groups, According to Subgroups.

The restricted full analysis set was used for this analysis. This set comprises all patients from the full analysis set (i.e., patients in the intention-to-treat population) with the exception of patients who had confirmed microalbuminuria at baseline (visit 1) and patients without any follow-up measurements of microalbuminuria that could be evaluated. All the results are based on adjudicated end points. The primary efficacy end point (the time to the onset of microalbuminuria) was analyzed with the use of a Cox proportional-hazards regression model, with study treatment as the fixed effect and the $\log_{10}$-transformed baseline urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) as the covariate. Owing to a prespecified interim analysis performed by the data and safety monitoring board, the significance level for the final confirmatory analysis was adjusted to 0.049, resulting in a two-sided 95.1% confidence interval. For all other analyses, two-sided 95% confidence intervals are shown. The sensitivity analyses were performed by extending the main model by an additional covariate. The exploratory subgroup analyses were performed with the use of the main model, with the exception of the subgroup analysis of urinary albumin-to-creatinine ratio. In this last analysis, the Cox proportional-hazards regression model with study treatment as the fixed effect was used.

better control of diabetes (glycated hemoglobin levels of ≤7.3 mg per deciliter), a lower level of renal function (estimated GFR of <84 ml per minute per 1.73 m²), and a urinary albumin-to-creatinine ratio of more than 4. During the double-blind treatment period, systolic and diastolic blood pressures were lower in the olmesartan group than in the placebo group by approximately 3.1/1.9 mm Hg.

Our findings extend the results of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT),[10] in which ACE inhibition with trandolapril was associated with a 53% decrease in the rate of microalbuminuria in patients with hypertension and type 2 diabetes. The greater treatment effect in BENEDICT is probably due to higher baseline and follow-up blood pressures; a post hoc analysis showed that the benefit occurred in patients with a systolic blood pressure higher than 139 mm Hg during follow-up.[17] The mean baseline blood pressure in the ROADMAP study was 136/81 mm Hg, and the target blood pressure (<130/80 mm Hg) was achieved by month 48 in nearly 80% of the patients taking olmesartan and 71% of those taking placebo. In both groups, antihypertensive drugs other than blockers of the renin–angiotensin system were added as needed. In contrast, only 14% of the subjects

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

* All results were based on adjudicated end points. The composite secondary efficacy end points were analyzed with the use of a Cox proportional-hazards regression model with study treatment as the fixed effect. For composite end points, the time to the onset of an event was defined as the time from randomization (date of visit 1) to the first occurrence of any component of the composite end point. CABG denotes coronary-artery bypass grafting.

in BENEDICT reached this level of blood-pressure control.[17] The results of the current study also differ somewhat from those of the Renin–Angiotensin System Study (RASS; ClinicalTrials.gov number, NCT00143949)[12] and the Diabetic Retinopathy Candesartan Trials (DIRECT; ClinicalTrials.gov numbers, NCT00252733, NCT00252720, and NCT00252694),[11] which did not show a protective effect of ARBs or ACE inhibitors against the development of microalbuminuria in patients with type 1 diabetes and in patients with type 2 diabetes, respectively, despite a substantial reduction in blood pressure. In both of these studies, the baseline systolic blood pressure was quite low — 133 mm Hg in DIRECT-Renal and 120 mm Hg in RASS.[11] Other studies, such as the Heart Outcomes and Prevention Evaluation (HOPE),[18] the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND; NCT00153101),[19] and the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation study (ADVANCE; NCT00145925),[20] had previously reported a positive relation between baseline systolic blood pressure and microalbuminuria. Thus, overall, it appears that the higher the baseline blood pressure, the greater the potential benefit of an inhibitor of the renin–angiotensin system.[10,11,18-20]

The greater tendency for patients with a lower estimated GFR (<83.8 ml per minute per 1.73 m^2) or a urinary albumin-to-creatinine ratio at the high end of the normal range (>4) to have a greater benefit with olmesartan is also of potential interest. This trend was also seen in TRANSCEND[19] and may help to identify patients with type 2 diabetes and no microalbuminuria who might be potential candidates for ARB therapy.

Changes in the GFR were minimal over the course of the study; olmesartan was associated

with a slight but significant reduction in the estimated GFR (about 4 ml per minute per 1.73 m²), whereas an even smaller decrease in the estimated GFR was noted in patients treated with agents that do not block the renin–angiotensin system. It is reassuring that the rate of renal events (defined as a doubling of the serum creatinine level or the need for dialysis) was low and was identical in the olmesartan and placebo groups. There was no washout period at the end of the study, so we can only speculate about whether the drop in the estimated GFR and the lower rate of microalbuminuria in the olmesartan group represent a favorable hemodynamic (functional) response to lower glomerular pressure or an adverse underlying structural change. Recent studies suggest that a low estimated GFR and microalbuminuria are independent prognostic markers.[14,15,21] In a meta-analysis,[21] an estimated GFR below 60 ml per minute per 1.73 m² was predictive of death from any cause and of death from cardiovascular causes, but as in the present trial, there was no relationship to the risk of cardiovascular disease when the estimated GFR was 75 to 104 ml per minute per 1.73 m². This supports the notion that in patients with diabetes, the observed change in the rate of microalbuminuria might in the long-term be of greater importance than the small fall in the estimated GFR.

The rates of cardiovascular and cerebrovascular events in the present study were low (about 4%, or 2.9 cases per 1000 person-years); they were similar to those in BENEDICT but lower than those in DIRECT-2 (8.0 cases per 1000 person years)[10,11] and substantially lower than those in studies involving patients with more advanced renal disease, such as the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetes Nephropathy Trial (IDNT), in which the rates were higher by a factor of approximately 20, or 60 cases per 1000 person-years.[8,9]

Despite the low rates of cardiovascular events, there were more deaths from cardiovascular causes in the olmesartan group than in the placebo group (15 vs. 3, P=0.01). Owing to the very small number of affected patients, it is difficult to interpret this unexpected finding, and it may simply be related to chance. Nevertheless, because of its potential significance, several exploratory analyses were performed. Fatal cardiovascular events were more common in the olmesartan group than in the placebo group among patients with known preexisting coronary heart disease (11 events vs. 1 with placebo, P=0.03), but the rates were similar in the two groups among patients without preexisting coronary disease. There was also a trend toward more fatal events in patients with preexisting coronary heart disease who were either in the lowest quartile of blood pressure or in the highest quartile of blood-pressure reduction during follow-up. Therefore, excessive reduction of blood pressure in some high-risk patients may confer a predisposition to an increased risk of death, a finding that is consistent with the well-known, somewhat controversial "J-curve effect"; however, a direct effect of olmesartan cannot be ruled out.

In the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT; NCT00141453), which involved

Table 3. Adverse Events That Occurred during Treatment.

Adverse Event	Olmesartan (N=2232)	Placebo (N=2215)	P Value*
	no. of patients (%)		
At least one serious event	335 (15.0)	337 (15.2)	0.85
At least one drug-related event†	255 (11.4)	166 (7.5)	<0.001
At least one serious drug-related event	4 (0.2)	1 (<0.1)	0.18
Most frequently reported events‡			
Hypertension	164 (7.3)	178 (8.0)	0.39
Headache	100 (4.5)	153 (6.9)	<0.001
Nasopharyngitis	112 (5.0)	94 (4.2)	0.22
Bronchitis	102 (4.6)	104 (4.7)	0.22
Influenza	80 (3.6)	98 (4.4)	0.15
Back pain	96 (4.3)	75 (3.4)	0.11
Dizziness	103 (4.6)	61 (2.8)	0.001
Peripheral edema	60 (2.7)	86 (3.9)	0.03
Events of special interest			
Hypotension	58 (2.6)	6 (0.3)	<0.001
Hyperkalemia	11 (0.5)	8 (0.4)	0.50

* P values were calculated with the use of a chi-square test.
† An event was considered to be drug-related if, according to the investigator's judgment, the event was definitely, probably, or possibly related to the treatment or if information on the relationship of the event to the study treatment was missing.
‡ Events included in this category are those that occurred in at least 3% of the patients in either study group; adverse events that were part of the primary or secondary efficacy end points are not shown.

patients with diabetic nephropathy, the addition of olmesartan to preexisting antihypertensive treatment was associated with a higher rate of death from cardiovascular causes (10 cases vs. 3 cases; www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm215222.htm). Because of these findings in ROADMAP and ORIENT, the Food and Drug Administration is currently reviewing existing data. Nevertheless, the rate of nonfatal cardiovascular events was not increased with olmesartan among patients without preexisting coronary heart disease. The results of the current study must also be viewed in the context of the many other studies of renal and cardiovascular outcomes that have shown that ARBs have a beneficial effect on cardiovascular disease.[22,23]

In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET; NCT00153101)[24] and the International Verapamil SR Trandolapril Study (INVEST; NCT00133692),[25] an increase in the rate of death from cardiovascular causes was observed among patients with known coronary heart disease if the systolic blood pressure was below 120 mm Hg during the time the patient was receiving therapy with ACE inhibitors or ARBs (in ONTARGET) or calcium-channel blockers or beta-blockers (in INVEST); thus, any adverse effect appears to be related more closely to the achieved blood pressure than the class of drug that was used. The concern about potential overtreatment is reflected in the guidelines published by the European Society of Hypertension, which state that physicians should avoid lowering blood pressure excessively (i.e., to values below 120/70 mm Hg) in persons with underlying cardiovascular disease.[26]

Our study has certain limitations. First, it is not possible to draw definite conclusions from a short-term prevention study about the way in which changes in microalbuminuria may affect the rates of renal and cardiovascular event rates in the long term. During the study itself, the follow-up period was too short. Second, the rate of premature withdrawals in both study groups was high (about 23% in both groups); however, it seems unlikely that withdrawals affected the overall findings of the study, since an exploratory analysis excluding these patients did not affect the primary end point. Third, although the differences in blood pressure between the treatment groups may have contributed to the primary outcome, and the benefit was greater in patients with higher baseline blood pressure, adjustment of the analysis for differences in blood pressure during the study did not eliminate the improvement in the primary end point that was seen with olmesartan.

In summary, this trial suggests that olmesartan increases the time to the onset of microalbuminuria in patients with type 2 diabetes, even when blood-pressure control is excellent according to current recommendations.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

- - -

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION : MDL NO. 2606

- - -

August 23, 2016

- - -

PROTECTED INFORMATION

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Videotape Rule 30(b)(6) deposition of DAIICHI SANKYO, INC., taken through its representative JEFFREY WARMKE, Ph.D., taken pursuant to notice, was held at the law offices of Drinker Biddle & Reath, LLP, 600 Campus Drive, Florham Park, New Jersey, beginning at 9:32 a.m., on the above date, before Kimberly A. Cahill, a Federally Approved Registered Merit Reporter and Notary Public for the State of New Jersey.

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people attending steering committee meetings for a scientific clinical study?
A. Michael Thiel was noted as ad hoc in the steering committee charter. Again, because -- and typically in a clinical development program, you're doing phase two and phase three clinical studies, targeting a product profile that you would want to bring to market, and commercial or new product planning would participate in those discussions.
Q. So the purpose -- well, the -- rephrase.
The purpose of the ROADMAP study was to -- ultimately, if things worked out, to expand the indications for the olmesartan drugs; correct?
A. There had been some preliminary discussions with BfArM, the regulatory authority in Germany, about the study. There was a potential that the study could have been filed, but it would be dependent on the results of the study.

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Q. As a result of the ROADMAP study, were the indications for the olmesartan drugs ever expanded?
A. No.
Q. Did Daiichi-Sankyo ever attempt to utilize the ROADMAP data to expand the indications for any of the olmesartan drugs?
A. No.
Q. And that's nowhere anywhere in the world?
A. Daiichi-Sankyo did not seek regulatory approval for an indication to prevent microalbuminuria anywhere in the world.
Q. Was the -- rephrase.
Were the results of the ROADMAP study ever utilized in a promotional manner by any Daiichi-Sankyo entity?
A. No.
Q. That would be improper. Right?
A. Correct.

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Q. And it would be improper from a regulatory standpoint; correct?
A. It would be improper from a regulatory standpoint, yes.
Q. In essence, that would be promotion of the drug for an off-label use; correct?
A. Correct.
Q. Which is illegal. Right?
A. Right. It's my understanding, yes.
Q. So we're going to go through, obviously, the ROADMAP study in some level of detail, but the net of it was, whatever data was generated, Daiichi-Sankyo never took that data to a regulatory authority to say, look, this now proves that the indications should be expanded. That never happened. Right?
A. Following completion of the ROADMAP study, individuals of Daiichi-Sankyo Europe did visit BfArM again to share the results with BfArM and discuss how BfArM viewed those data.

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Q. BfArM is the regulatory entity in Germany?
A. Correct.
Q. And just for the record, it's B-P-H-A-R-M. That's what you're saying. Right?
A. B-F-A-R-M.
Q. Oh, okay.
A. There's no P.
Q. Okay. I had a memory of seeing it. I guess I was --
A. I know.
Q. -- wrong. So after the ROADMAP study was -- rephrase.
Was it the at the conclusion of the ROADMAP study that BfArM was approached or was the study still ongoing?
A. There were discussions with BfArM before the study was completed and after the study was completed.
Q. Who participated in the discussions after the study was completed?

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BY MR. SLATER:
Q. Did Daiichi-Sankyo in the United States make any contact with the FDA regarding the potential for seeking an expansion of indications?
A. Not to my knowledge.
Q. Did your company make any inquiry to any regulatory authority outside Germany regarding the possibility of expanding the indications for the drug based on the ROADMAP study?
A. I did not review any regulatory correspondence in Japan, so I cannot answer yes or no to that question in Japan.
Q. Coming back off our major tangent, looking at the people who signed the protocol for the ROADMAP study, there's someone named Yu Haag, H-A-A-G, Ph.D., vice director, head of biostatistics and data management, Sankyo in Europe.
Who's that person?
A. He was the head of the

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biostatistics group for the Sankyo Europe.
Q. There's a signature line for an F Freischlager, head of clinical data management and biostatistics at INFORM. And that was the CRO?
A. INFORM was the CRO, yes.
Q. And by signing onto this -- rephrase.
By signing onto this protocol, each of the signatories on behalf of their organizations are agreeing that the design of this protocol is acceptable and agreeing to abide by it; correct?
A. They're agreeing that the design of the protocol is acceptable, yes.
Q. And the design of the protocol is part of the design of the study; correct?
A. The design of the protocol dictates the design of the study. The conduct of the study had other documents

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that were supplemental to the protocol, yes.
Q. Looking at the protocol, I'm going to work off of the Bates numbers to begin with. Okay?
A. Okay.
Q. Those are the numbers in the bottom right. Do you see that?
A. Uh-hum.
Q. Look to the page that says 932. Those are the last three digits? At the top, it says "Synopsis."
A. Okay.
Q. The protocol number is listed under the title of the study and that's just the internal number used within Sankyo?
A. For protocol numbering, yes.
Q. This is a phase IIIb study. What does that technically mean?
A. For -- there is no universal definition of a IIIb study across the industry. Different companies and different organizations use that term

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differently.
Within Daiichi-Sankyo Europe specifically, the IIIb designation is given to a clinical study conducted after approval of the initial indication for a treatment that is not in the current label. The purpose of the study may or may not be to seek regulatory approval.
Q. The objectives that are listed are the reasons why the study was conducted; correct?
A. Yes, the primary objective and the exploratory secondary objectives, yes.
Q. The primary objective of the study was in essence to see if the use of olmesartan medoxomil could prevent or at least delay microalbuminuria from developing; correct?
A. Yes, to look at the time to occurrence of microalbuminuria in diabetic patients.
Q. Ah. Okay. The -- we'll go through it in a little more detail, but

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the patients that were being studied were diabetic; correct?
A. Yes.
Q. The secondary objectives, you referred to them as exploratory. Tell me what you mean by exploratory.
A. In -- without going into great statistical detail --
Q. Please don't.
A. -- the -- endpoints can be viewed as either confirmatory or exploratory.
Confirmatory endpoints are based on inference -- inference, confidence, and statistical significance. Exploratory endpoints typically are looking for patterns. They are hypothesis-generating analyses used to identify areas for future exploration.
In this case, the ROADMAP study was statistically powered to see a 30 percent reduction in microalbuminuria. The study was not powered to see statistically significant differences in

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the exploratory endpoints.
Q. And I'm certainly not going to ask you a statistical math question, because I'm less qualified than you are and you're probably much more qualified than I'll ever be understanding the statistics, but I want to understand, just in layman's terms, what you just said. I think I do but -- and then we'll move on from it.
When you point out that the study was statistically powered to show a 30 percent reduction in microalbuminuria -- let me start over.
When you say the study was statistically powered to show a 30 percent reduction in this condition, which I'm going to refer to as MA as we move forward, that means that statisticians analyzed how many patients would we need, what would be the numbers that would have to be found to have either this result or that result to reach certain endpoints; correct?

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A. The statistician predefined that they would need to see 326 events of microalbuminuria to demonstrate a 30 percent difference in the treatment effect, and that would require the enrollment of approximately 4,400 patients.
Q. The study was not statistically powered to study any of the secondary endpoints; correct?
A. Correct.
Q. And that would include just observation of adverse events as they may be reported; correct?
A. Correct.
Q. The secondary endpoints are essentially -- and they're listed here in the protocol -- medical issues that were of interest to be looked at in the study; correct?
A. Yes, microalbuminuria is recognized as a risk factor for development of end stage renal disease and also increased risk of cardiovascular

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disease, so there were exploratory analyses to evaluate the impact of olmesartan in this study on both renal and cardiac events.
Q. On the pages that are 934 and 935 is a discussion of the population of patients that would be studied and the major inclusion and exclusion criteria; correct?
A. Yes.
Q. If I understand correctly, this is documentation of the fact that in designing the study, you wanted to study a certain profile of patients in order to get data that you thought would be most useful?
A. Yes.
Q. And that inclusion and exclusion criteria would create a -- essentially a subset of patients to be studied that would not be the same as the patients out in the field that would be using olmesartan; correct?
MR. PARKER: Objection.

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protocol did not define asking specific questions about any specific organ class -- organ classes.
Q. The CRFs, the case report forms, do not list anywhere to fill in specific information about any gastrointestinal-related side effects; correct?
A. The case report forms contain a place to report all reported AEs.
Q. There's no place in the case report forms that actually specifically calls out gastrointestinal side effects or related issues. That's not something specifically asked for in the case report form; correct?
A. Correct.
Q. The ROADMAP study was not designed to study gastrointestinal side effects of olmesartan; correct?
A. The primary endpoint of the ROADMAP study was the prevention of microalbuminuria. As part of the study,

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all reported safe -- AEs were collected.
MR. SLATER: Move to strike from "As" forward.
BY MR. SLATER:
Q. The ROADMAP study was not designed to specifically study gastrointestinal side effects of olmesartan; correct?
A. Gastrointestinal events was not one of the prespecified endpoints in ROADMAP.
Q. And it -- gastrointestinal side effects was not the primary endpoint, obviously, and was not a specifically called out secondary endpoint; correct?
A. Gastrointestinal events was not a predefined endpoint in the study.
Q. At any point, did anybody at Daiichi-Sankyo inform Professor Haller or any of the other investigators about postmarketing adverse events that were being received by the company in connection with gastrointestinal side

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effects?
A. No. Professor Haller was clear that he received no communication from Daiichi-Sankyo regarding the potential for gastrointestinal side effects up to and including the time he wrote his letter to the Mayo Clinic.
Q. Did Professor Haller see any patients who had gastrointestinal side effects in his treatment of patients over the years? Did you ask him that when you met with him?
A. I did not ask him that specific question.
Q. Did he tell you anything along that line?
A. He did not volunteer that he had personally witnessed any patients taking olmesartan with gastrointestinal side effects and, in fact, indicated that based on his review of the safety data throughout the course of the ROADMAP study, there was never an issue raised about gastrointestinal side effects by

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the steering committee or by the data safety monitoring committee.
Q. And just to be clear, there was never a time where anyone from Daiichi-Sankyo informed Professor Haller or the other investigators or the steering committee that reports were coming in of gastrointestinal side effects, some being categorized as celiac disease during a period of time; that was not -- that information was not provided to them; correct?
A. As I said before, Professor Haller indicated that he had not received any communications from Daiichi-Sankyo highlighting gastrointestinal side effects.
Q. Would that hold true for the steering committee as well and the other investigators?
A. I did not interview all the steering committee members during my investigation, but Professor Haller indicated that he had not been informed

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I'm not going to go through the whole e-mail, but at the bottom of B, she says, "It is almost impossible to design a late-phase clinical trial with a proper sample size that can detect all real safety signals with conformity as designed, one that can detect the real signal for primary efficacy endpoint with conformity."

Do you see what I just read?

A. Yeah, I see that sentence.

Q. And that's just a statistical analysis of why it would be that you wouldn't look to the data that was supplied by the ROADMAP study to try to determine whether there's an increased risk of cardiac -- cardiovascular mortality because it's just not what was being looked at in this study. Right?

A. I'm going to have to defer that question to the statistical expert.

Q. If you go to the very first e-mail, the first page, there's an e-mail now from Antonia Wang and she points out

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in part, the danger of conducting a small study in this case for cardiovascular event is seen all the time. She speaks through it a little bit more and at the end says, without proper preplanning and appropriate sample size, we can get some results that is inconclusive; correct?

A. Yes.

Q. And certainly there was no effort to establish a sample size large enough to study the question of cardiovascular mortality. That's not what the study was geared for. Right?

A. The ROADMAP study was sized and powered to detect a 30 percent difference in the occurrence of microalbuminuria. It was not powered and sized to detect a meaningful difference in clinical outcomes.

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(Deposition Exhibit No. 3035, 3/4-3/5/10 E-Mail Chain Among Caspard, Cuprys, et al, OLM-DSI-0003999681 and

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OLM-DSI-0003999682, was marked for identification.)

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MR. PARKER: I want to take a break. We've been going for about an hour and 20 minutes.

MR. SLATER: Okay.

MR. PARKER: Okay?

THE VIDEO TECHNICIAN: The time is 2:31 p.m. We are going off the record.

(A recess was taken from 2:31 p.m. to 2:45 p.m.)

- - -

THE VIDEO TECHNICIAN: This is DVD number 4. The time is 2:45 p.m. Back on the record.

BY MR. SLATER:

Q. I've handed you Exhibit 3035, which is some e-mails that address in part the ROADMAP study. Do you see that?

A. Yes, I see the e-mail.

Q. I'm going to just start

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right at the top of the first page, an e-mail from Herve Caspard in pharmacovigilance to Rich Cuprys and Allen Feldman.

Do you see that e-mail at the top?

A. Yes.

Q. Who's Rich Cuprys?

A. Rich Cuprys was in regulatory affairs in the United States.

Q. Herve Caspard writes to him and is talking about a slide presentation and then says towards the bottom that Bill Bailey -- and he's someone in medical affairs; correct?

A. Yes.

Q. -- that Bill Bailey should send me today market research data that will likely be relevant, stressing that the ROADMAP population is very different from the general population treated with olmesartan in the U.S. I would like to consolidate this information in a backup slide.

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exists. Right?
A. No, I do not.
Q. The reason it matters is this -- well, I'll get to it.
Whatever it says in this letter to the editor, I'm not going to walk through the whole letter, he was doing a statistical analysis based on a comparison of the two arms of the study; correct -- well, let me actually ask it differently.
What Professor Haller and Menne did in this letter is, they talked about going back and looking at the data to see if there were intestinal effects in either arm and what was found; correct?
A. He was looking for a difference of incidence of GI AEs between the treatment group and the placebo group.
Q. That was not a subject that was studied, correct, specifically? It wasn't an endpoint at all; correct?

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A. It was not a predefined endpoint.
Q. The study was not powered to evaluate that question. Right?
A. That's correct.
Q. And, in fact, we went through some language in the context of the cardiovascular mortality issue where Glenn Gormley in a white paper and in an internal document actually talked about the fact that you can't draw definitive conclusions about that secondary endpoint because of the way the study was designed. It just -- it's not set up to study that issue.
The same would hold true for gastrointestinal effects probably even to a larger extent. Right?
MR. PARKER: Objection; form.
THE WITNESS: There was not a prespecified endpoint for GI AEs in the study, that's correct.
BY MR. SLATER:

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Q. Nowhere in this letter to the editor to the Mayo Clinic does Dr. Menne or Dr. Haller talk about any of the olmesartan side patients who I showed you today their documentation; that's not discussed here at all. Right?
MR. PARKER: Objection.
MR. SLATER: Let me ask it differently.
BY MR. SLATER:
Q. The specifics of patients who developed or were documented to develop gastrointestinal effects, that's not discussed in detail here. Right?
A. The specifics of patients who developed gastrointestinal AEs in either the olmesartan or the placebo group are not described here.
MR. SLATER: Let's go off the video for a second.
THE VIDEO TECHNICIAN: Sure. The time is 4:31 p.m. Off the record.
- - -

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(A discussion off the record occurred.)
- - -
THE VIDEO TECHNICIAN: The time is 4:41 p.m. Back on the record.
- - -
EXAMINATION
- - -
BY MR. PARKER:
Q. Dr. Warmke, good afternoon. It's now 20 to 5:00. It's been a long day, but I have a few questions I need to ask you to address some of the issues that Mr. Slater reviewed with you today during the course of your deposition. Okay?
A. Okay.
Q. Let's begin where we started today with your qualifications; and I'm not going to repeat anything that's been said, but tell the jury what experience you have professionally with clinical trial.